APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the de-&al route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name:	Diazinon
CAS number:	333-41-5
Date:	August 1996
Profile status:	Final
Route:	[X] Inhalation [ ] Oral
Duration:	[ ] Acute [X] Intermediate [ ] Chronic
Key to figure:	5
Species:	Rat
MRL:	0.009 [ ] mg/kg/day [ ] ppm [xl mg/m^3
Reference:	Hartman HR (1990) 21 -day repeated exposure inhalation toxicity in the rat. Project

No. 891205. An unpublished report dated June 8, 1990 from Ciba-Geigy Basel/Switzerland. EPA-41557402.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): This is a 21-day repeated exposure inhalation toxicity to diazinon using a nose-only exposure system. Four groups of albino rats (10 males [15 l-200 g] and 10 females [142-179 g] each) were exposed to various concentrations of aerosol diazinon (0,0.05,0.46, 1.57, and 11.6 mg/m^3) diluted in ethanol for 6 hours a day, 5 days a week for 3 weeks. Particle size analysis was done to ensure that the test aerosols were in the respirable range for the rat. Two control groups were used, one exposed to humidified filtered air only and the other to the carrier vehicle ethanol (21.54 g/m^3). The test substance was the liquid MG-8 formulation (88% diazinon). Exposure levels were monitored by gas chromatography. Clinical examinations included ophthalmology, body weight, food consumption, hematology, and blood chemistry (including serum cholinesterase and erythrocyte acetylcholinesterase). The termination of the exposure period was followed by gross necropsy, brain acetylcholinesterase, organ weight determination, and histopathology of the nasal tissues and lungs from all groups and the spleen, heart, liver, kidney, adrenal gland, and any tissue with gross lesions from the control and 11.6 mg/m^3 groups.

Effects noted in study and corresponding doses:
No deaths or changes in body weights or food consumption were observed. Piloerection was observed in most animals, particularly during the first week into the exposure, with the incidence gradually declining during weeks 2 and 3 of exposure. This sign was neither exposure nor dose-related and no clinical signs of organophosphate toxicity were observed. No exposure-related ophthalmoscopic or histopathological lesions were found (nasal tissues and lungs, spleen, heart, liver, kidney, and adrenal gland). Minimally lower values of red blood cell parameters (erythrocyte count, hemoglobin, and packed red cell volume) were observed in the highest dose (11.6 mg/m^3) females but were not statistically significant. A statistically significant higher lung to body weight ratio was observed in the females only at.exposures of 0.46 and 1.57 mg/m^3 but not at 11.6 mg/m^3. Since no histopathological evidence of adverse effects to the lung was reported, the toxicological significance of this finding is uncertain. Statistically significant reductions at study termination in serum cholinesterase (marker for exposure) were seen in males at 1.57 mg/m^3 (14%) and 11.6 mg/m^3 (19%) and in females at 0.46 mg/m^3 (20%), 1.57 mg/m^3 (27%), and 11.6 mg/m^3 (43%). Statistically significant reductions in erythrocyte acetylcholinesterase (surrogate marker for neural acetylcholinesterase) were seen in males at 11.6 mg/m^3 (36%) and in females at 1.57 mg/m^3 (10%) and 11.6 mg/m^3 (39%). Statistically significant reductions in brain acetyl-

cholinesterase were not seen in males, but were seen in females at 0.05 mg/m^3 (24%), 0.46 mg/m^3 (17%), 1.57 mg/m^3 (20%), and 11.6 mg/m^3 (37%).

Effect of Aerosol Diazinon on Cholinesterase Activities

	Serum ChE	Erythrocyte AChE	Brain AChE
Males (week 4)			
0.05 mg/m^3	+9%**	+2%	-1%
0.46 mg/m3	-5%	-5%	+1%
1.57 mg/m3	-14%*	-6%	-4%
11.6 mg/m^3	-19%*	-36%**	-3%
Females (week 4)			
0.05 mg/m3	-3%	-1%	-24%**
0.46 mg/m3	-20%*	+6%	-17%*
1.57 mg/m^3	-27%**	-10%*	-20%*
11.6 mg/m^3	-43%**	-39%**	-37%**

* statistically significantly different from control ($p \leq 0.05$); ** ($p \leq 0.01$).

No evidence of a dose-response effect for diazinon is seen for males in this study. However, a dose-response for inhibition of both erythrocyte and brain acetylcholinesterase occurred in the females at the 1.57 and 11.6 mg/m^3 levels. A NOAEL of 0.46 mg/m^3 for inhibition of neural acetylcholinesterase is used for the derivation of the MRL.

Dose end point used for MRL derivation:

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [X] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
These conversion factors were taken from Interim Methods for Development of Inhalation Reference

Concentrations, Appendix H (EPA 1990). Inhibition of brain acetylcholinesterase is considered an Extrarespiratory effect.

The Mass Median Aerodynamic Diameter (MMAD) was reported as a lower limit of 0.8 μm and an upper limit of 1.2 μm for an average of 1.0 μm (pg 33 Hartman 1990). The Geometric Standard Deviation (GSD) was reported as a lower limit of 1.2 μm and an upper limit of 1.5 μm for an average of 1.35 or 1.4 μm. The Regional Deposited Dose Ratio (RDDR) from Table H1 under the ER (Extrarespiratory effects) column is 0.0076. This ratio is adjusted by the body weight ratio between humans and female rats (0.166 kg reported). Thus: $RDDR_{[ADJ]}$ = 0.0076 x (70 kg/0.166 kg) (EPA 1988 values for human body weight) = 3.2048

Using Equation 4-7 and 0.0076 for $RDDR_{ER}$ in Table H-1 (MMAD = 0.1, Sigma g = 1.4) in EPA (1990 - Interim Methods for Development of Inhalation Reference Concentrations), and correcting by the body weight ratios, the $NOAEL_{[HEC]}$ is calculated:

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RDDR_{ER}$

$NOAEL_{[HEC]} = (0.46\ mg/m^3 \times 6\ hr/d/24\ hr \times 5\ d/7\ d) \times (0.0076 \times 70\ kg/0.166\ kg)$

$NOAEL_{[HEC]} = 0.082\ mg/m^3 \times 3.2048$

$NOAEL_{[HEC]} = 0.2628\ mg/m^3$

Thus,

$MRL = NOAEL_{[HEC]} \div UF$

$MRL = 0.2628\ mg/m^3 \div (3 \times 10)$

$MRL = 0.2628\ mg/m^3 \div 30$

$MRL = 9x10^{-3}\ mg/m^3 = 0.009\ mg/m^3$

Was a conversion used from intermittent to continuous exposure?
If so, explain: Yes. Exposure was for 21 days, 6 hours a day 5 days a week.
$NOAEL_{[ADJ]}$ = (0.46) x (6 hours a day/24 hours) x (5 days/7 days) = (0.082 mg/m^3)

Other additional studies or pertinent information that lend support to this MRL:
This is the only available well conducted intermediate-duration inhalation study for diazinon. In an acute-duration study in which rats were exposed to 2,300 mg/m^3 diazinon for four hours (Holbert 1989), mild signs of organophosphate toxicity were noted (nasal discharge, salivation). NIOSH recommends an occupational exposure level of 0.1 mg/m^3, approximately 100-fold higher than the MRL.

Agency Contact (Chemical Manager): Alfred Dorsey

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name:	Diazinon
CAS number(s):	333-41-5
Date:	August 1996
Profile Status:	Final
Route:	[ ] Inhalation [x] Oral
Duration:	[ ] Acute [x] Intermediate [ ] Chronic
Key to figure:	64
Species:	Dog

MRL. 0.0002 [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Barnes TB (1988) 90-Day oral toxicity study in dogs. Unpublished report submitted by Ciba-Geigy, Summit NJ dated August 4, 1988. EPA 40815004.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): The purpose of this study was to determine the 13-week oral toxicity profile of diazinon in male and female beagle dogs. Diazinon was added to standard canine ration at concentrations of 0, 0.1, 0.5, 150, and 300 ppm. The test substance was the MG-8 formulation of diazinon (87.7% pure) mixed with feed and adjusted for purity. The concentrations of diazinon in the feed were determined during weeks 1, 3,5,9, and 13. Each dog was supplied with approximately 400 g of food daily. The corresponding doses, in mg/kg, were calculated by the authors to be 0.0034,0.02,5.9, and 10.9 in males and 0.0037, 0.021, 5.6, and 11.6 in females. Four dogs per sex were assigned to each dose level. After receipt, dogs were allowed approximately six weeks to acclimate. During the acclimation period, body weight and food consumption were measured, and clinical laboratory measurements (hematology, serum chemistry, and urinalysis) and physical, auditory, and ophthalmoscopic exams were performed. Upon initiation of the study, appearance, mortality and clinical observations were monitored daily, while body weight and food consumption were monitored weekly; clinical laboratory measurements were performed at weeks 5 and 9. Physical, auditory, and ophthalmoscopic exams and clinical laboratory measurements were performed prior to termination. A complete necropsy was performed on all animals, and the following organs were collected for histopathological examination: adrenals, brain (cerebral cortex, cerebellar cortex, medulla/pans), epididymides, heart, kidneys, liver, lungs, ovaries, peripheral (sciatic) nerve, pituitary, prostate, salivary (mandibular), spinal cord (cervical, lumbar, thoracic), spleen, testes, thymus, thyroid (with parathyroids), and uterus. After being weighed, a portion of each brain was utilized for determining levels of acetylcholinesterase activity by a calorimetric method. Tissue samples were preserved for subsequent histological examination.

Effects noted in study and corresponding doses:

No deaths occurred during the study. Treatment-related reductions in body weight gain of 34 and 33%, respectively, were noted in the 5.6 mg/kg females and 10.9 mg/kg males, respectively. Clinical signs included emesis and diarrhea, but were not dose related. No pathology of any nervous system tissue (brain, spinal cord, sciatic nerve) was noted under either gross or microscopic examination.

Statistically significant, dose-related decreases in serum cholinesterase levels (marker for exposure to diazinon) were noted in males and females beginning at doses of 0.02 and 5.6 mg/kg, respectively. Significant reductions in erythrocyte and brain acetylcholinesterase levels were noted in males and

females beginning at the 5.9 and 5.6 mg/kg levels. No change was observed in blood drawn on day 12. On days 29, 56, and 86 erythrocyte acetylcholinesterase declined by 26, 25, and 25% in males and 31, 31, and 31% in females (pp 202–204 for males, pp 257–259 for females). Levels in the highest dose group were similar. Brain samples analyzed at the termination of the study showed reduction of acetylcholinesterase activity of 31% in males at 5.9 mg/kg/day and 42% at 10.9 mg/kg/day. Female brain acetylcholinesterase activity was reduced 30% at 5.6 mg/kg/day and 45% at 11.6 mg/kg/day.

Effect of Diazinon on Cholinesterase Activity (mUnits/mL)

Dose (mg/kg/day)	Serum ChE	Erythrocyte AChE	Brain AChE
Males (Day 86)			
0	2199.5	2950	2067.5
0.0034	1809 (-18%)	3025 (+3%)	1982.5 (-4%)
0.02	1536 (-30%)*	2425 (-18%)	2150 (+4%)
5.9	430.5 (-80%)**	2225 (-25%)**	1432.5 (-31%)**
10.9	335.75 (-85%)**	2025 (-31%)**	1195 (-43%)**
Females (Day 86)			
0	2137.5	3075	2056.7
0.0037	2237.25 (+5%)	3075 (0%)	2137.5 (+4%)
0.021	1824.75 (-15%)	2950 (-4%)	2110 (+3%)
5.6	398.25 (-81%)**	2125 (-31%)**	1442.5 (-30%)**
11.6	355.75 (-83%)**	2125 (-31%)**	1130 (-45%)**

* significantly different from control ($p \leq 0.05$); ** ($p \leq 0.01$)

A NOAEL of 0.02 mg/kg/day is apparent for the neurological endpoint of brain AChE inhibition in both males and females.

Dose endpoint used for MRL derivation:

[x] NOAEL [ ] LOAEL

MINIMAL RISK LEVEL (MRL) WORKSHEET

Uncertainty factors used in MRL derivation:

[] 1 []3 [] 10(foruseofaLOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

MRL=NOAEL+UF

MRL = 0.02 mg/kg/day /100

MRL = 0.0002 mg/kg/day

Was a conversion factor used from uum in food or water to a mg/bodv weight dose?
If so, explain: NA

If an inhalation studv in animals. list conversion factors used in determining human eauivalent dose: NA

Was a conversion used from intermittent to continuous exposure?
If so, explain: NA

Other additional studies or nertinent information that lend support to this MRL:
This study, along with the Singh (1988) study in rats, are the best available for intermediate-duration oral exposure in laboratory animals. A dose-response relationship was demonstrated for inhibition of the neurological target of diazinon, neural acetylcholinesterase. A NOAEL of 0.019 mg/kg/day was also determined in mongrel dogs in a 12-week oral-exposure study (Williams et al. 1959).

Agency Contact (Chemical Manager): Alfred Dorsey

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upperbound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

APPENDIX B

(2) Exposure Period Three exposure periods - acute (less than 1.5 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "1%" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health" covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.0005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less'Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg /kg/day.

(16) NOAEL In this example, 18, NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.0005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk-levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

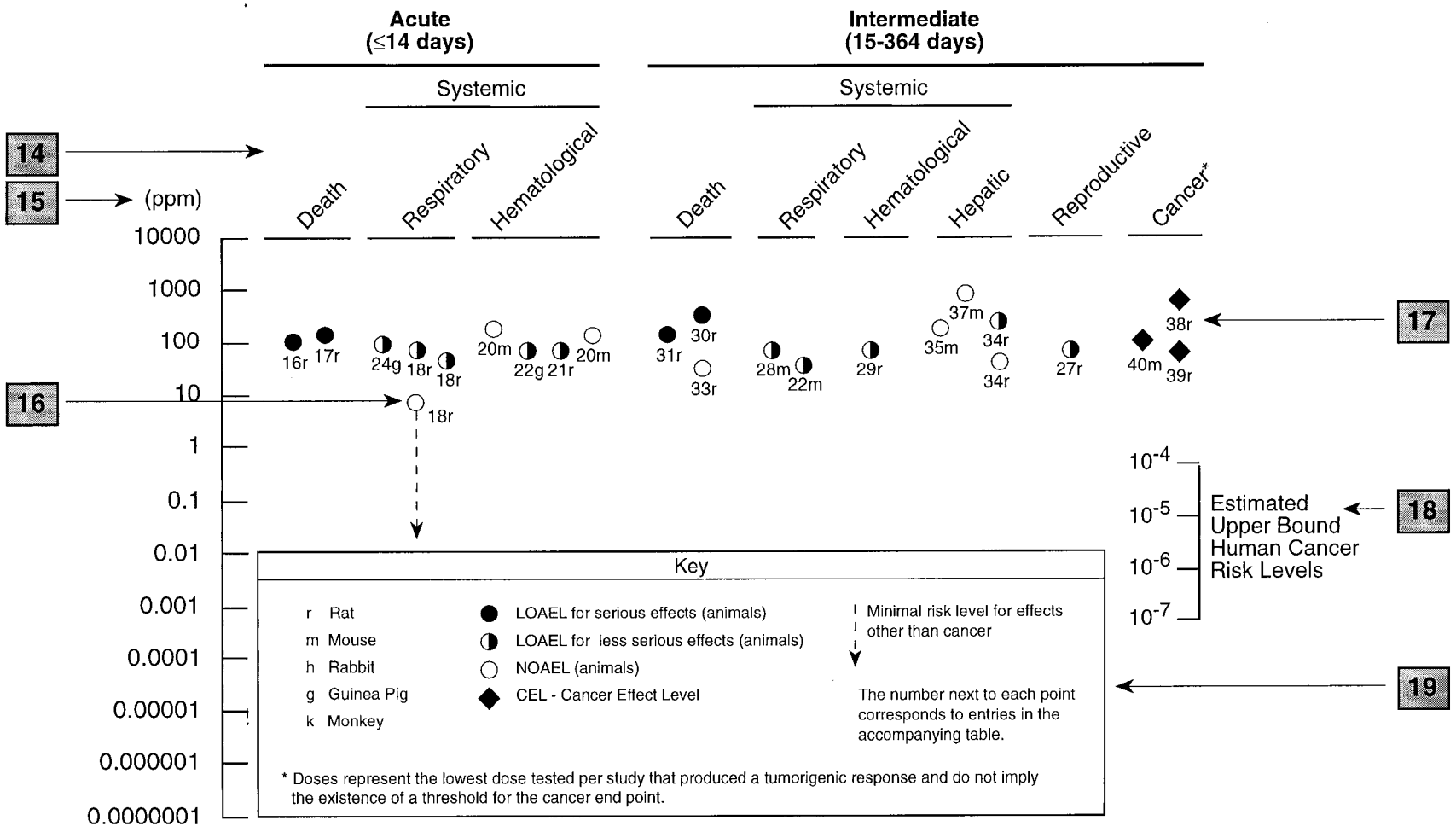
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
					↓		
Cancer							
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX B

Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Substances,” and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

APPENDIX B

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

• U.S. GOVERNMENT PRINTING OFFICE: 1996-739-324